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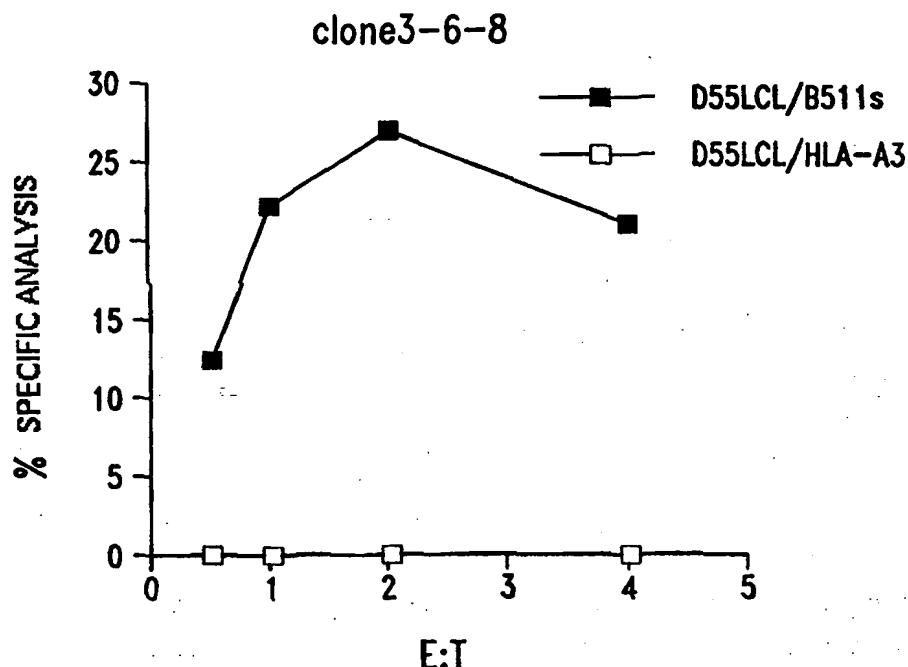
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<p>(71) Applicant: CORIXA CORPORATION [US/US]; Suite 200, 1124 Columbia Street, Seattle, WA 98104 (US).</p> <p>(72) Inventors: REED, Steven, G.; 2843 – 122nd Place Northeast, Bellevue, WA 98005 (US). XU, Jiangchun; 15805 Southeast 43rd Place, Bellevue, WA 98006 (US).</p> <p>(74) Agents: MAKI, David, J. et al.; Seed and Berry LLP, 6300 Columbia Center, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).</p>															

(54) Title: COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

(57) Abstract

Compounds and methods for the treatment and diagnosis of breast cancer are provided. The inventive compounds include polypeptides containing at least a portion of a breast tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of breast cancer comprising such polypeptides, or polynucleotide molecules encoding such polypeptides, are also provided, together with polynucleotide molecules for preparing the inventive polypeptides.



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COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment and diagnosis of breast cancer. The invention is more particularly related to polypeptides comprising at least a portion of a protein that is preferentially expressed in breast tumor tissue and to polynucleotide molecules encoding such polypeptides. Such polypeptides may be used in vaccines and pharmaceutical compositions for treatment of breast cancer. Additionally such polypeptides and polynucleotides may be used in the immunodiagnosis of breast cancer.

BACKGROUND OF THE INVENTION

Breast cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and treatment of the disease, breast cancer remains the second leading cause of cancer-related deaths in women, affecting more than 180,000 women in the United States each year. For women in North America, the life-time odds of getting breast cancer are now one in eight.

No vaccine or other universally successful method for the prevention or treatment of breast cancer is currently available. Management of the disease currently relies on a combination of early diagnosis (through routine breast screening procedures) and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular breast cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. *See, e.g.,* Porter-Jordan and Lippman, *Breast Cancer* 8:73-100 (1994). However, the use of established markers often leads to a result that is difficult to interpret, and the high mortality observed in breast cancer patients indicates that improvements are needed in the treatment, diagnosis and prevention of the disease.

Accordingly, there is a need in the art for improved methods for therapy and diagnosis of breast cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

The present invention provides compounds and methods for immunotherapy of breast cancer. In one aspect, isolated polypeptides are provided comprising at least an immunogenic portion of a breast tumor protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein the breast tumor protein comprises an amino acid sequence encoded by a polynucleotide molecule having a partial sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52 and 55-67, 72, 73, and 89-94, (b) complements of said nucleotide sequences and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

In related aspects, isolated polynucleotide molecules encoding the above polypeptides are provided. In specific embodiments, such polynucleotide molecules have partial sequences provided in SEQ ID NOS: 3, 10, 17, 24, 45-52 and 55-67, 72, 73, and 89-94. The present invention further provides expression vectors comprising the above polynucleotide molecules and host cells transformed or transfected with such expression vectors. In preferred embodiments, the host cells are selected from the group consisting of *E. coli*, yeast and mammalian cells.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known breast antigen.

The present invention also provides pharmaceutical compositions comprising at least one of the above polypeptides, or a polynucleotide molecule encoding such a polypeptide, and a physiologically acceptable carrier, together with vaccines comprising at least one or more such polypeptide or polynucleotide molecule in combination with a non-specific immune response enhancer. Pharmaceutical compositions and vaccines comprising one or more of the above fusion proteins are also provided.

In related aspects, pharmaceutical compositions for the treatment of breast cancer comprising at least one polypeptides and a physiologically acceptable carrier are provided, wherein the polypeptide comprises an immunogenic portion of a breast tumor protein or a variant thereof, the breast tumor protein being encoded by a polynucleotide molecule having a partial sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, and 74-88, (b) complements of said nucleotide sequences, and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions. The invention also provides vaccines for the treatment of breast cancer comprising such polypeptides in combination with a non-specific immune response enhancer, together with pharmaceutical compositions and vaccines comprising at least one polynucleotide molecule having a partial sequence provided in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, and 74-88.

In yet another aspect, methods are provided for inhibiting the development of breast cancer in a patient, comprising administering an effective amount of at least one of the above pharmaceutical compositions and/or vaccines.

The present invention also provides methods for immunodiagnosis of breast cancer, together with kits for use in such methods. In one specific aspect of the present invention, methods are provided for detecting breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the inventive polypeptides; and (b) detecting in the sample a protein or polypeptide that binds to the binding agent. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody.

In related aspects, methods are provided for monitoring the progression of breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as diagnostic kits

comprising such antibodies, and methods of using such antibodies to inhibit the development of breast cancer.

The present invention further provides methods for detecting breast cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a DNA molecule that encodes one of the above polypeptides; and (c) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers. In a preferred embodiment, at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a DNA molecule having a partial sequence selected from the group consisting of SEQ ID NOS: 1-94.

In a further aspect, the present invention provides a method for detecting breast cancer in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe specific for a polynucleotide molecule that encodes one of the above polypeptides; and (c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe. Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a DNA molecule having a partial sequence selected from the group consisting of SEQ ID NOS: 1-94.

In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A and B show the specific lytic activity of a first and a second B511S-specific CTL clone, respectively, measured on autologous LCL transduced with B511s (filled squares) or HLA-A3 (open squares).

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the immunotherapy and diagnosis of breast cancer. The inventive compositions are generally isolated polypeptides that comprise at least a portion of a breast tumor protein. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents."

In particular, the subject invention discloses polypeptides comprising at least a portion of a human breast tumor protein, or a variant thereof, wherein the breast tumor protein includes an amino acid sequence encoded by a polynucleotide molecule including a sequence selected from the group consisting of: nucleotide sequences recited in SEQ ID NOS: 1- 94, the complements of said nucleotide sequences, and variants thereof. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above breast proteins may consist entirely of the portion, or the portion may be present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous, and such sequences may be immunoreactive and/or antigenic.

As used herein, an "immunogenic portion" of a human breast tumor protein is a portion that is capable of eliciting an immune response in a patient inflicted with breast cancer and as such binds to antibodies present within sera from a breast cancer patient. Such immunogenic portions generally comprise at least about 5 amino acid residues, more preferably at least about 10, and most preferably at least about 20 amino acid residues. Immunogenic portions of the proteins described herein may be identified in antibody binding assays. Such assays may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A. Alternatively, a polypeptide may be used to generate

monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of breast cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known in the art and include those summarized in Paul, *Fundamental Immunology*, 3rd ed., Raven Press, 1993, pp. 243-247.

The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments.

The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides. A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the therapeutic, antigenic and/or immunogenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution, deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described below) to the identified polypeptides.

As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids

represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also, or alternatively, contain other modifications, including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydrophobic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions or additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA*, 2:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity (determined as described below) to the recited sequence.

The antigens provided by the present invention include variants that are encoded by DNA sequences which are substantially homologous to one or more of the DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

Two nucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, more preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) Optimal alignments in linear space *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method for reconstructing phylogenetic trees *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Rapid similarity searches of nucleic acid and protein data banks *Proc. Natl. Acad. Sci. USA* 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by

determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Also included in the scope of the present invention are alleles of the genes encoding the nucleotide sequences recited herein. As used herein, an "allele" or "allelic sequence" is an alternative form of the gene which may result from at least one mutation in the nucleic acid sequence. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. Any given gene may have none, one, or many allelic forms. Common mutational changes which give rise to alleles are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone or in combination with the others, one or more times in a given sequence.

For breast tumor polypeptides with immunoreactive properties, variants may, alternatively, be identified by modifying the amino acid sequence of one of the above polypeptides, and evaluating the immunoreactivity of the modified polypeptide. For breast tumor polypeptides useful for the generation of diagnostic binding agents, a variant may be identified by evaluating a modified polypeptide for the ability to generate antibodies that detect the presence or absence of breast cancer. Such modified sequences may be prepared and tested using, for example, the representative procedures described herein.

The breast tumor proteins of the present invention, and polynucleotide molecules encoding such proteins, may be isolated from breast tumor tissue using any of a variety of methods well known in the art. Polynucleotide sequences corresponding to a gene (or a portion thereof) encoding one of the inventive breast tumor proteins may be isolated from a breast tumor cDNA library using a subtraction technique as described in detail below. Examples of such DNA sequences are provided in SEQ ID NOS: 1- 94. Partial polynucleotide sequences thus obtained may be used to design oligonucleotide primers for the amplification of full-length polynucleotide sequences in a polymerase chain reaction (PCR), using techniques well known in the art (see, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY,

1989). Once a polynucleotide sequence encoding a polypeptide is obtained, any of the above modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA*, 2:183, 1983).

The breast tumor polypeptides disclosed herein may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (see, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Alternatively, any of the above polypeptides may be produced recombinantly by inserting a polynucleotide sequence that encodes the polypeptide into an expression vector and expressing the protein in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a polynucleotide molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as CHO cells. The polynucleotide sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in an isolated, substantially pure form (*i.e.*, the polypeptides are homogenous as determined by amino acid composition and primary sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments,

described in more detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known breast tumor antigen, together with variants of such fusion proteins.

A polynucleotide sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble separate polynucleotide sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a polynucleotide sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a polynucleotide sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated polynucleotide sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of polynucleotides are located only 5' to the polynucleotide sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the polynucleotide sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. *New Engl. J. Med.*, 336:86-91 (1997)).

Polypeptides of the present invention that comprise an immunogenic portion of a breast tumor protein may generally be used for immunotherapy of breast cancer, wherein the polypeptide stimulates the patient's own immune response to breast tumor cells. In further aspects, the present invention provides methods for using one or more of the immunoreactive polypeptides encoded by a polynucleotide molecule having a sequence provided in SEQ ID NOS: 1- 94 (or fusion proteins comprising one or more such polypeptides and/or polynucleotides encoding such polypeptides) for immunotherapy of breast cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease. Accordingly, the above immunoreactive polypeptides (or fusion proteins or polynucleotide molecules encoding such polypeptides) may be used to treat breast cancer or to inhibit the development of breast cancer. The polypeptides may be administered either prior to or following surgical removal of primary tumors and/or treatment by administration of radiotherapy and conventional chemotherapeutic drugs.

In these aspects, the polypeptide or fusion protein is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more of such polypeptides and a non-specific immune response enhancer, wherein the non-

specific immune response enhancer is capable of eliciting or enhancing an immune response to an exogenous antigen. Examples of non-specific-immune response enhancers include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of breast tumor antigens, either incorporated into a combination polypeptide (i.e., a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

Alternatively, a pharmaceutical composition or vaccine may contain polynucleotides encoding one or more of the above polypeptides, such that the polypeptide is generated *in situ*. In such pharmaceutical compositions and vaccines, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary polynucleotide sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an epitope of a breast tumor cell antigen on its cell surface. In a preferred embodiment, the polynucleotide molecules may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *PNAS* 91:215-219, 1994; Kass-Eisler et al., *PNAS* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating polynucleotides into such expression systems are well known to those of ordinary skill in the art. The polynucleotides may also be "naked," as described, for example, in published PCT application WO 90/11092, and Ulmer et al., *Science* 259:1745-1749, 1993, reviewed by Cohen, *Science* 259:1691-1692,

1993. The uptake of naked polynucleotides may be increased by coating the polynucleotides onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or polynucleotide molecule that is effective to raise an immune response (cellular and/or humoral) against breast tumor cells in a treated patient. A suitable immune response is at least 10-50% above the basal (*i.e.*, untreated) level. In general, the amount of polypeptide present in a dose (or produced *in situ* by the polynucleotide in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 μ g. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum

hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ).

Polypeptides disclosed herein may also be employed in adoptive immunotherapy for the treatment of cancer. Adoptive immunotherapy may be broadly classified into either active or passive immunotherapy. In active immunotherapy, treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (for example, tumor vaccines, bacterial adjuvants, and/or cytokines).

In passive immunotherapy, treatment involves the delivery of biologic reagents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (for example, CD8+ cytotoxic T-lymphocyte, CD4+ T-helper, tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells and macrophages) expressing the disclosed antigens. The polypeptides disclosed herein may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Patent No. 4,918,164), for passive immunotherapy.

The predominant method of procuring adequate numbers of T-cells for adoptive immunotherapy is to grow immune T-cells *in vitro*. Culture conditions for expanding single antigen-specific T-cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. These *in vitro* culture conditions typically utilize intermittent stimulation with antigen, often in the presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted above, the immunoreactive polypeptides described herein may be used to rapidly expand antigen-specific T cell cultures in order to generate sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B-cells, may be pulsed with immunoreactive polypeptides or transfected with a polynucleotide sequence(s), using standard techniques well known in the art. For example, antigen presenting cells may be transfected with a

polynucleotide sequence, wherein said sequence contains a promoter region appropriate for increasing expression, and can be expressed as part of a recombinant virus or other expression system. For cultured T-cells to be effective in therapy, the cultured T-cells must be able to grow and distribute widely and to survive long term *in vivo*. Studies have demonstrated that cultured T-cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever, M., et al, "Therapy With Cultured T Cells: Principles Revisited," *Immunological Reviews*, 157:177, 1997).

The polypeptides disclosed herein may also be employed to generate and/or isolate tumor-reactive T-cells, which can then be administered to the patient. In one technique, antigen-specific T-cell lines may be generated by *in vivo* immunization with short peptides corresponding to immunogenic portions of the disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard tissue culture techniques, and returned to the patient.

Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective *in vitro* stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example, by Chang et al. (*Crit. Rev. Oncol. Hematol.*, 22(3), 213, 1996). Cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, WA) CEPRATE™ system (see U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

In another embodiment, T-cell and/or antibody receptors specific for the polypeptides can be cloned, expanded, and transferred into other vectors or effector cells for use in adoptive immunotherapy.

In a further embodiment, syngeneic or autologous dendritic cells may be

pulsed with peptides corresponding to at least an immunogenic portion of a polypeptide disclosed herein. The resulting antigen-specific dendritic cells may either be transferred into a patient, or employed to stimulate T cells to provide antigen-specific T cells which may, in turn, be administered to a patient. The use of peptide-pulsed dendritic cells to generate antigen-specific T cells and the subsequent use of such antigen-specific T cells to eradicate tumors in a murine model has been demonstrated by Cheever et al, *Immunological Reviews*, 157:177, 1997).

Additionally, vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

Polypeptides of the present invention may also, or alternatively, be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human breast tumors. Binding agents of the present invention may generally be prepared using methods known to those of ordinary skill in the art, including the representative procedures described herein. Binding agents are capable of differentiating between patients with and without breast cancer, using the representative assays described herein. In other words, antibodies or other binding agents raised against a breast tumor protein, or a suitable portion thereof, will generate a signal indicating the presence of primary or metastatic breast cancer in at least about 20% of patients afflicted with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without primary or metastatic breast cancer. Suitable portions of such breast tumor proteins are portions that are able to generate a binding agent that indicates the presence of primary or metastatic breast cancer in substantially all (*i.e.*, at least about 80%, and preferably at least about 90%) of the patients for which breast cancer would be indicated using the full length protein, and that indicate the absence of breast cancer in substantially all of those samples that would be negative when tested with full length protein. The representative assays described below, such as the two-antibody sandwich assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human breast tumors.

The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human breast tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic breast cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate antibodies capable of detecting at least 20% of primary or metastatic breast tumors by such procedures are considered to be useful in assays for detecting primary or metastatic human breast tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human breast tumors may be used as markers for diagnosing breast cancer or for monitoring disease progression in patients. In one embodiment, breast cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera and urine.

The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (*i.e.*, in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation

exceeds about 10^3 L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome with or without a peptide component, an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, or monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-grafted or humanized. Antibodies may be prepared by the methods described herein and by other methods well known to those of skill in the art.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner is indicative of the reactivity of the sample with the immobilized binding partner.

The solid support may be any material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as

adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μ g, and preferably about 100 ng to about 1 μ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20TM (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior

to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with breast cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include enzymes (such as horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of antibody to reporter group may be achieved using standard methods known to those of ordinary skill in the art.

The second antibody is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound second antibody is then removed and bound second antibody is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of breast cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the

cut-off value is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without breast cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for breast cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for breast cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of breast cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of antibody immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody

sandwich assay, in the format discussed above. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above descriptions are intended to be exemplary only.

In another embodiment, the above polypeptides may be used as markers for the progression of breast cancer. In this embodiment, assays as described above for the diagnosis of breast cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, breast cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, breast cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.*

6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate breast tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitzer), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Diagnostic reagents of the present invention may also comprise polynucleotide sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify breast tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a DNA molecule encoding a breast tumor protein of the present invention. The presence of the amplified

cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a DNA molecule encoding a breast tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a biological sample.

As used herein, the term "oligonucleotide primer/probe specific for a DNA molecule" means an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the DNA molecule in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10 contiguous nucleotides of a DNA molecule having a partial sequence selected from SEQ ID NOS: 1- 94. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a DNA molecule having a partial sequence provided in SEQ ID NOS: 1- 94. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis *et al. Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to detect breast tumor-specific sequences in biological samples, including blood, urine and/or breast tumor tissue.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES

This Example describes the isolation of breast tumor polypeptides from a breast tumor cDNA library.

A human breast tumor cDNA expression library was constructed from a pool of breast tumor poly A⁺ RNA from three patients using a Superscript Plasmid System for

cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, breast tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A⁺ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BstX I adaptors (Invitrogen, Carlsbad, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA 94303), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen, Carlsbad, CA) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human breast cDNA expression library was prepared from a pool of four normal breast tissue specimens. The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The breast tumor library contained 1.14×10^7 independent colonies, with more than 90% of clones having a visible insert and the average insert size being 936 base pairs. The normal breast cDNA library contained 6×10^6 independent colonies, with 83% of clones having inserts and the average insert size being 1015 base pairs. Sequencing analysis showed both libraries to contain good complex cDNA clones that were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination sequencing.

cDNA library subtraction was performed using the above breast tumor and normal breast cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a breast tumor-specific subtracted cDNA library was generated as follows. Normal breast cDNA library (70 μ g) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μ l of H₂O, heat-denatured and mixed with 100 μ l (100 μ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA), the resulting mixture was irradiated with a 270 W sunlamp

on ice for 20 minutes. Additional Photoprobe biotin (50 μ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μ l H₂O to form the driver DNA.

To form the tracer DNA, 10 μ g breast tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μ l H₂O. Tracer DNA was mixed with 15 μ l driver DNA and 20 μ l of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μ l H₂O, mixed with 8 μ l driver DNA and 20 μ l of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK⁺ (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a breast tumor specific subtracted cDNA library.

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted breast tumor specific library and characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Thirty-eight distinct cDNA clones were found in the subtracted breast tumor-specific cDNA library. The determined 3' cDNA sequences for 14 of these clones are provided in SEQ ID NO: 1-14, with the corresponding 5' cDNA sequences being provided in SEQ ID NO: 15-28, respectively. The determined one strand (5' or 3') cDNA sequences for the remaining clones are provided in SEQ ID NO: 29-52. Comparison of these cDNA sequences with known sequences in the gene bank using the EMBL and GenBank databases (Release 97) revealed no significant homologies to the sequences provided in SEQ ID NO: 3, 10, 17, 24 and 45-52. The sequences provided in SEQ ID NO: 1, 2, 4-9, 11-16, 18-23, 25-41, 43 and 44 were found to show at least some degree of

homology to known human genes. The sequence of SEQ ID NO: 42 was found to show some homology to a known yeast gene.

Data was analyzed using Synteni provided GEMTOOLS Software. Twenty one distinct cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested. The determined partial cDNA sequences for these clones are provided in SEQ ID NO: 53- 73. Comparison of the sequences of SEQ ID NO: 53, 54, and 68-71 with those in the gene bank as described above, revealed some homology to previously identified human genes. No significant homologies were found to the sequences of SEQ ID NO: 55-67, 72 (referred to as JJ 9434,7117), and 73 (referred to as B535S).

In a further experiment, cDNA fragments analyzed by DNA microarray were obtained from two subtraction libraries derived by conventional subtraction, as described above. In one instance the tester was derived from primary breast tumors. In the second instance, a metastatic breast tumor was employed as the tester. Drivers consisted of normal breast.

cDNA fragments from these two libraries were submitted as templates for DNA microarray analysis. DNA chips were analyzed by hybridizing with fluorescent probes derived from mRNA from both tumor and normal tissues. Analysis of the data was accomplished by creating three groups from the sets of probes. The composition of these probe groups, referred to as Breast Tumor/mets, Normal non-breast tissues, and Metastatic breast tumors. Two comparisons were performed using the modified Gemtools analysis. The first comparison was to identify templates with elevated expression in breast tumors. The second was to identify templates not recovered in the first comparison that yielded elevated expression in metastatic breast tumors. An arbitrary level of increased expression (mean of tumor expression versus the mean of normal tissue expression) was set at approximately 2.2.

In the first round of comparison to identify overexpression in breast tumors, two novel gene sequences were identified, hereinafter referred to as B534S and B538S (SEQ ID NO: 89 and 90), and six sequences that showed some degree of homology to previously identified genes (SEQ ID NO: 74-79). Additionally, in a second comparison to identify elevated expression in metastatic breast tumors, five novel sequences were identified, hereinafter referred to as B535S (overexpressed in this analysis as well as what was described

above), B542S, B543S, P501S, and B541S (SEQ ID NO: 73, and 91-94), as well as nine gene sequences that showed some homology to known genes (SEQ ID NO: 80-88). Clone B534S and B538S (SEQ ID NO: 89 and 90) were shown to be overexpressed in both breast tumors and metastatic breast tumors.

Example 2

GENERATION OF HUMAN CD8+ CYTOTOXIC T-CELLS THAT RECOGNIZE ANTIGEN PRESENTING CELLS EXPRESSING BREAST TUMOR ANTIGENS

This Example illustrates the generation of T cells that recognize target cells expressing the antigen B511S, also known as 1016-F8 (SEQ ID NO: 56). Human CD8+ T cells were primed *in-vitro* to the B511S gene product using dendritic cells infected with a recombinant vaccinia virus engineered to express B511S as follows (also see Yee et al., Journal of Immunology (1996) 157 (9):4079-86). Dendritic cells (DC) were generated from peripheral blood derived monocytes by differentiation for 5 days in the presence of 50 µg/ml GMCSF and 30 µg/ml IL-4. DC were harvested, plated in wells of a 24-well plate at a density of 2×10^5 cells/well and infected for 12 hours with B511S expressing vaccinia at a multiplicity of infection of 5. DC were then matured overnight by the addition of 3 µg/ml CD40-Ligand and UV irradiated at $100\mu\text{W}$ for 10 minutes. CD8+ T cells were isolated using magnetic beads, and priming cultures were initiated in individual wells (typically in 24 wells of a 24-well plate) using 7×10^5 CD8+ T cells and 1×10^6 irradiated CD8-depleted PBMC; IL-7 at 10 ng/ml was added to cultures at day 1. Cultures were re-stimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with B511S and the costimulatory molecule B7.1. Cultures were supplemented at day 1 with 15 I.U. of IL-2. Following 4 such stimulation cycles, CD8+ cultures were tested for their ability to specifically recognize autologous fibroblasts transduced with B511S using an interferon- γ Elispot assay (see Lalvani et al J. Experimental Medicine (1997) 186:859-965). Briefly, T cells from individual microcultures were added to 96-well Elispot plates that contained autologous fibroblasts transduced to express either B511S or as a negative control antigen EGFP, and incubated overnight at 37° C; wells also contained IL-12 at 10 ng/ml. Cultures were identified that specifically produced interferon- γ only in response to B511S transduced

fibroblasts; such lines were further expanded and also cloned by limiting dilution on autologous B-LCL retrovirally transduced with B511S. Lines and clones were identified that could specifically recognize autologous B-LCL transduced with B511S but not autologous B-LCL transduced with the control antigens EGFP or HLA-A3. An example demonstrating the ability of human CTL cell lines derived from such experiments to specifically recognize and lyse B511S expressing targets is presented in Figure 1.

Example 3
SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on an Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS

1. An isolated polypeptide comprising an immunogenic portion of a breast protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, and 89-94; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.
2. An isolated polynucleotide molecule comprising a nucleotide sequence encoding the polypeptide of claim 1.
3. An isolated polynucleotide molecule comprising a sequence provided in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, and 89-94.
4. An expression vector comprising a polynucleotide molecule according to any one of claims 2 and 3.
5. A host cell transformed with the expression vector of claim 4.
6. The host cell of claim 5 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.
7. A pharmaceutical composition comprising the polypeptide of claim 1 and a physiologically acceptable carrier.
8. A vaccine comprising the polypeptide of claim 1 and a non-specific immune response enhancer.

9. The vaccine of claim 8 wherein the non-specific immune response enhancer is an adjuvant.

10. A vaccine comprising a polynucleotide molecule of any one of claims 2 and 3 and a non-specific immune response enhancer.

11. The vaccine of claim 10 wherein the non-specific immune response enhancer is an adjuvant.

12. A pharmaceutical composition for the treatment of breast cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, and 74-88; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

13. A vaccine for the treatment of breast cancer comprising a polypeptide and a non-specific immune response enhancer, said polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, and 74-88; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

14. The vaccine of claim 13 wherein the non-specific immune response enhancer is an adjuvant.

15. A vaccine for the treatment of breast cancer comprising a polynucleotide molecule and a non-specific immune response enhancer, the polynucleotide

molecule comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, and 74-88; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

16. The vaccine of claim 15, wherein the non-specific immune response enhancer is an adjuvant.

17. A pharmaceutical composition according to claims 7 or 12, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

18. A vaccine according to any one of claims 8, 10, 13 or 15, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

19. A fusion protein comprising at least one polypeptide according to claim 1.

20. A pharmaceutical composition comprising a fusion protein according to claim 19 and a physiologically acceptable carrier.

21. A vaccine comprising a fusion protein according to claim 19 and a non-specific immune response enhancer.

22. The vaccine of claim 21 wherein the non-specific immune response enhancer is an adjuvant.

23. A pharmaceutical composition according to claim 20, for use in manufacture of a medicament for inhibiting the development of breast cancer in a patient.

24. A vaccine according to claim 21, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

25. A method for detecting breast cancer in a patient, comprising:

(a) contacting a biological sample from a patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-94, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-94 under moderately stringent conditions; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting breast cancer in the patient.

26. The method of claim 25 wherein the binding agent is a monoclonal antibody.

27. The method of claim 26 wherein the binding agent is a polyclonal antibody.

28. A method for monitoring the progression of breast cancer in a patient, comprising:

(a) contacting a biological sample from a patient with a binding agent that is capable of binding to a polypeptide, said polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-94, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-94 under moderately stringent conditions;

(b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b); and

(d) comparing the amount of polypeptide detected in steps (b) and (c) to monitor the progression of breast cancer in the patient.

29. A monoclonal antibody that binds to a polypeptide comprising an immunogenic portion of a breast protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein said protein comprises an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, and 89-94; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

30. A monoclonal antibody according to claim 29, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

31. The monoclonal antibody of claim 30 wherein the monoclonal antibody is conjugated to a therapeutic agent.

32. A method for detecting breast cancer in a patient comprising:

(a) contacting a biological sample from a patient with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a polynucleotide molecule encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-94, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-94 under moderately stringent conditions; and

(b) detecting in the sample a polynucleotide sequence that amplifies in the presence of the oligonucleotide primers, thereby detecting breast cancer.

33. The method of claim 32, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide molecule comprising a sequence selected from SEQ ID NOS: 1-94.

34. A diagnostic kit comprising:

- (a) one or more monoclonal antibodies of claim 29; and
- (b) a detection reagent.

35. A diagnostic kit comprising:

- (a) one or more monoclonal antibodies that bind to a polypeptide encoded by a polynucleotide molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, and 74-88, complements of said sequences and sequences that hybridize to a sequence of SEQ ID NO: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, or 74-88 under moderately stringent conditions; and

- (b) a detection reagent.

36. The kit of claims 34 or 35 wherein the monoclonal antibodies are immobilized on a solid support.

37. The kit of claim 36 wherein the solid support comprises nitrocellulose, latex or a plastic material.

38. The kit of claims 34 or 35 wherein the detection reagent comprises a reporter group conjugated to a binding agent.

39. The kit of claim 38 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

40. The kit of claim 38 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

41. A diagnostic kit comprising at least two oligonucleotide primers, at least one of the oligonucleotide primers being specific for a polynucleotide molecule encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein

comprising an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-94, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-94 under moderately stringent conditions.

42. A diagnostic kit of claim 41 wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide molecule comprising a sequence selected from SEQ ID NOS: 1-94.

43. A method for detecting breast cancer in a patient, comprising:
(a) obtaining a biological sample from the patient;
(b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide molecule encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-94, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-94 under moderately stringent conditions; and
(c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe, thereby detecting breast cancer in the patient.

44. The method of claim 43 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide molecule comprising a sequence selected from the group consisting of SEQ ID NOS: 1-94.

45. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide molecule encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide molecule comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-94, complements of said nucleotide sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1-94 under moderately stringent conditions.

46. The diagnostic kit of claim 45, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide molecule comprising a sequence selected from the group consisting of SEQ ID NOS: 1-94.

47. Peripheral blood cells from a patient incubated in the presence of at least one polypeptide of claim 1, such that T cells proliferate, for use in the manufacture of a medicament for treating breast cancer in a patient.

48. The blood cells of claim 47 wherein the T cells is repeated one or more times.

49. A composition for the treatment of breast cancer in a patient, comprising T cells proliferated in the presence of a polypeptide of claim 1, in combination with a pharmaceutically acceptable carrier.

50. An antigen presenting cells incubated in the presence of at least one polypeptide of claim 1, for use in the manufacture of a medicament for treating breast cancer in a patient.

51. The cells of claim 50 wherein the antigen presenting cells are selected from the group consisting of dendritic and macrophage cells.

52. A composition for the treatment of breast cancer in a patient, comprising antigen presenting cells incubated in the presence of a polypeptide of claim 1, in combination with a pharmaceutically acceptable carrier.

1/1

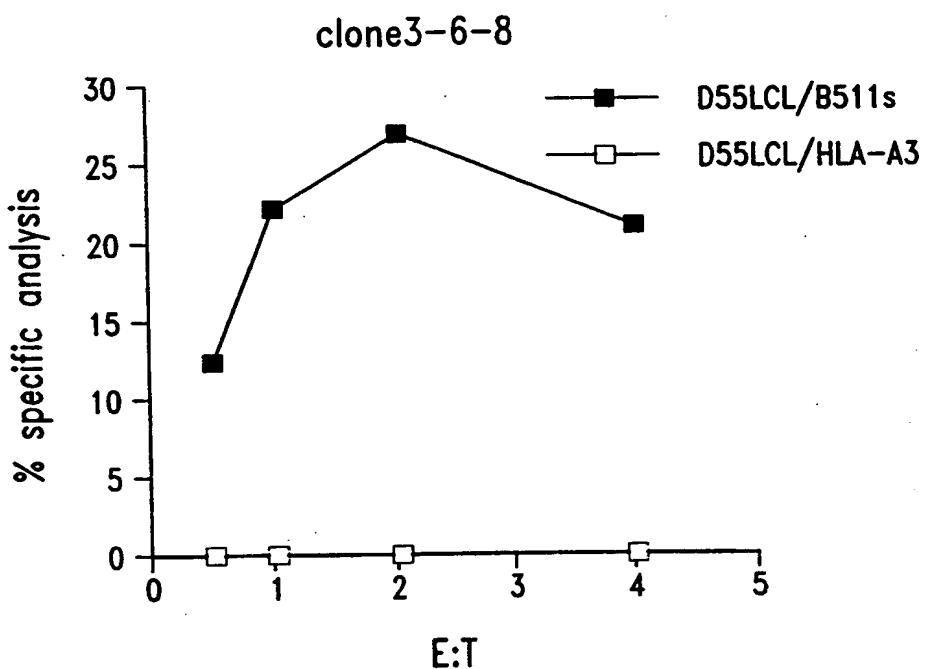


Fig. 1A

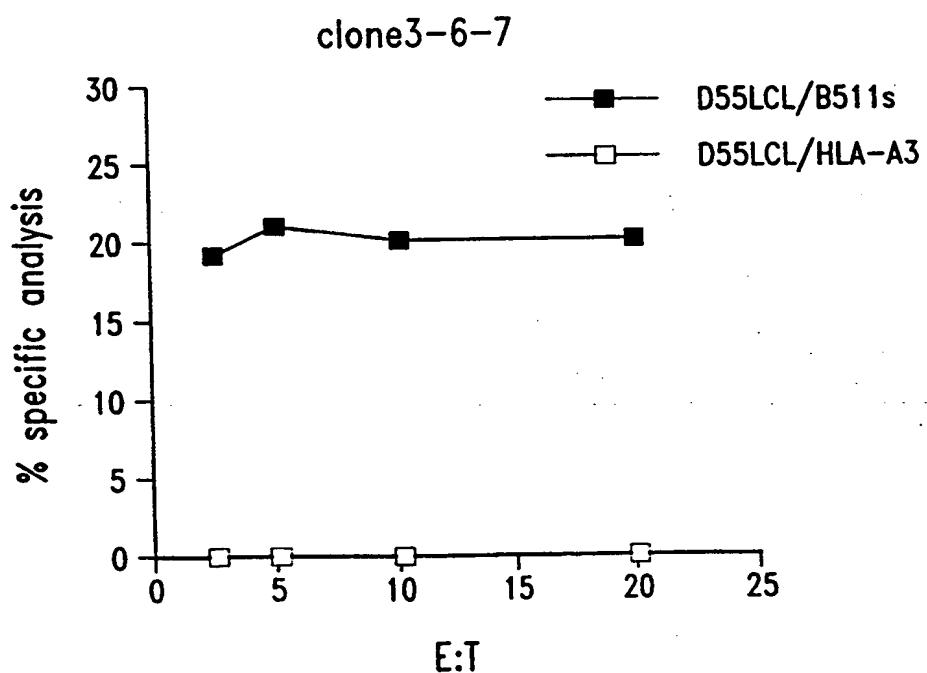


Fig. 1B

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<212> DNA
<213> Homo sapiens

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caggn 425

<210> 11
<211> 424
<212> DNA
<213> Homo sapiens

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gtccccnat tcttaangg ctnacactn ctcattcggg tnatgtgtc caattaaatc 360
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<210> 12
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<212> DNA
<213> Homo sapiens

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<211> 419
<212> DNA
<213> Homo sapiens

<400> 13
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<210> 14
<211> 400
<212> DNA
<213> Homo sapiens

<400> 14
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<210> 15
<211> 395
<212> DNA
<213> Homo sapiens

<400> 15

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ctntgttatt actgttggan ttttgatgct gcatgacaga ttttgcttan tgtaaaaatn 360
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<210> 16

<211> 404

<212> DNA

<213> Homo sapiens

<400> 16

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<210> 17

<211> 360

<212> DNA

<213> Homo sapiens

<400> 17

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acctcataacc tnaccgcttc cttttaatgc gccttcggtg tgcgcaca tggcacgtg 180
cggggagaac catacttatt cccctttcc cggcctacca cctctnctcc cccttctt 240
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cccgcaatta cctggcaaaa ctgcgcaccc ttccggcagc gctaaanaat gcacatttac 360

<210> 18

<211> 316

<212> DNA

<213> Homo sapiens

<400> 18

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agccagttt tcatttgctt aaatnactca ccaagtaact aattaagttn tctttactct 180
taatgttnag tagtgagatt ctgttgaagg tgatattaaa aaccattcta tattaattaa 240
cattcatgtt gttttttaaa agcttatttgg aaatcnaatt atgattattt ttcataccag 300
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<210> 19

<211> 350

<212> DNA

<213> Homo sapiens

<400> 19

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ccgttttagt agtcgcagac ctcgaaatga tagacgaaat gctccacctg taagaacaga 180
anatcgctt atagttgaga atttacctc aagagtcagc tggcagggtt gttganatac 240
agttttgagt tntttgatg tggctttta aaaaagttat gggttactna tgttatattg 300
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<210> 20

<211> 367

<212> DNA

<213> Homo sapiens

<400> 20

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ncaattntga cctnnggcga anaatggcng nnngtgcata gtntccnctc tgnggnctct 180
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ccaatttagtgcatgntanag cntcctggcc cagatggcnc ccatatcctg gtncggcttc 300
cgcccctacc angncatccn catctactag agcttacccg ctncntgngg cgcaccggnt 360
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<210> 21

<211> 366

<212> DNA

<213> Homo sapiens

<400> 21

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tcctttatct tctgaagaaa gtacacaccc tggtnatgat atcttgcataat tgcccttctt 180
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<210> 22

<211> 315

<212> DNA

<213> Homo sapiens

<400> 22

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caatatattt gtaaaaactg agatacangt ttgacccata tctgcatttt gataattaaa 180
cnaatnnatt ctattnaat gttgttcag agtcacagca cagactgaaa ctttttttga 240
atacctnaat atcacacttn tncttnnaat gatgttgaag acaatgtgatga catgccttna 300
gcatataatg tcgac 315

<210> 23

<211> 202

<212> DNA

<213> Homo sapiens

<400> 23

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aaatgttnca nnaaganatg acgctgattc tgnnaaatct tttcagaag atagaggaga 180
acacccaccc nttcatttt tg 202

<210> 24
<211> 365
<212> DNA
<213> Homo sapiens

<400> 24
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acggcactgc atctnaccctg acntggattt gaacccgggg tggcagcng aattgaacag 360
gatca 365

<210> 25
<211> 359
<212> DNA
<213> Homo sapiens

<400> 25
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aaccgcggca tcaacctgga gctctncccc ccgacntttaa ccttccntg tcttacttac 300
nttaaccgc gnttattttt cttnaaaaga actttcccc aatactttct ttcaccnnt 359

<210> 26
<211> 400
<212> DNA
<213> Homo sapiens

<400> 26
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ggtttctgtt ttcatcgtt aactctcaag agcttggaaat ttatcactcc catcctcact 180
acnacnaana aatctnaacn aacngaanac caatgacttt tcttagatct gtcaaagaac 240
ttcagccacg agggaaacta tcnccctnaa tactggggac tggaaagaga ggttacagag 300
aatcacagtg aatcatagcc caagatcagc ttgcccggag cttaagctng tacgatnatt 360
acttacaggg accacttcac agtnngtnga tnaantgccc 400

<210> 27
<211> 366
<212> DNA
<213> Homo sapiens

<400> 27
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gaattttaca ttttccagaa aacactcctt tctgtatctg tgaaagaaag tggcctcag 180
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agtattgatt ttcctcanac tcagcctgtg tagctntgaa agcatggaac agattacact 300
gcagtnacg tcatcccaca catcttgac tccnagaccc ggggaggtca catagtcgt 360
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<210> 28

<211> 402

<212> DNA

<213> Homo sapiens

<400> 28

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anagcttcaa ggcttcattc agggccttng ctnaggcgcc nctctccatc tccnggaata 360
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<210> 29

<211> 175

<212> DNA

<213> Homo sapiens

<400> 29

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ttcagccgct gcacgttgggt ctgcagggac tccgtggact tttccgcct cctcg 175

<210> 30

<211> 360

<212> DNA

<213> Homo sapiens

<400> 30

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gttctttcag ggaaccaaac ccagaattcg gtgaaaaggc caaacatctt ggtgggattt 300
gataaatgcc ttgggacactg gagtgttggg ctgtgcaca ggaagagcac cagccgctga 360

<210> 31

<211> 380

<212> DNA

<213> Homo sapiens

<400> 31

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tgaaaagtgcgca ctgcagtgat ggtcaangga gactcancat atgtgattgt tccntnataa 360
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<210> 32
<211> 440
<212> DNA
<213> Homo sapiens

<400> 32
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<210> 33
<211> 345
<212> DNA
<213> Homo sapiens

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tggtctgctg ggaatgttgt tgggggtt gggaaagantt atttc 345

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<212> DNA
<213> Homo sapiens

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<210> 35
<211> 540
<212> DNA
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<210> 36
<211> 555
<212> DNA
<213> Homo sapiens

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<210> 37
<211> 280
<212> DNA
<213> Homo sapiens

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<210> 38
<211> 303
<212> DNA
<213> Homo sapiens

<400> 38
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<213> Homo sapiens

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<210> 40
<211> 318
<212> DNA
<213> Homo sapiens

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<210> 41
<211> 302
<212> DNA
<213> Homo sapiens

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ccaaacnattt accagacatt cctttanat tgaaaacgga tntcttccc ttggcaaaga 300
tc 302

<210> 42
<211> 299
<212> DNA
<213> Homo sapiens

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<210> 43
<211> 305
<212> DNA
<213> Homo sapiens

<400> 43
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ctgcccattt ccggccggaaag gccttctcc actggtacac aggccaggc atggacaaga 180
tggagttcac cgaggcttag agcaacatga acgacactcgat ctctnagtat cagcagtagacc 240
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aggca 305

<210> 44

<211> 399
 <212> DNA
 <213> Homo sapiens

<400> 44
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 agaaggcagcn gcccgcgnaa ttngaagcng tttctgttgc cttgganaaa gaatttgagc 300
 ttctttatta ggcAACGAA aaACCCGAA ananaggcnt tacnataacct tngaaaantc 360
 tccngccnna aaaagaaaga agcttcnnga ttcttaacc 399

<210> 45
 <211> 440
 <212> DNA
 <213> Homo sapiens

<400> 45
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<210> 46
 <211> 472
 <212> DNA
 <213> Homo sapiens

<400> 46
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 ccactttctc acccccattc tcccccaat taactctcc tcatccccat gatgccattt 180
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 cctcataaca atctccctcc cagcctctac tgctgccttc tctgagtttct tcccagggtc 360
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 aaaaatgtcc atncntgtcc tggatgtat ctnccangna naataacaaa tt 472

<210> 47
 <211> 550
 <212> DNA
 <213> Homo sapiens

<400> 47
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 gggggccctg tctgggtgca aggcgcacage tgcctttctt caccaggcat cctcggcatg 180
 gtggagctgg cgcgtcagtc catcgtgtat gaactggcca tcattgtgtat catggccct 240
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 gaattctgct 550

<210> 48
 <211> 214
 <212> DNA
 <213> Homo sapiens

<400> 48
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 agtttgtgtt cagtttaag gtggggcagg gtacccgca tgatcccccc aaggtgaagt 180
 gtgagacnat ggtctatcac cccnacattt acct 214

<210> 49
 <211> 267
 <212> DNA
 <213> Homo sapiens

<400> 49
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 gtngaggaac ttaatccaaac cggagctntt gtgaaggtca gaanacagga gagggaatct 180
 tggcaaggaa tggagacnga gtttgc当地 tgcagctaga gttaatngtt ntaaatggga 240
 ctgctnttgc gtctcccang gaaagtt 267

<210> 50
 <211> 300
 <212> DNA
 <213> Homo sapiens

<400> 50
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<210> 51
 <211> 300
 <212> DNA
 <213> Homo sapiens

<400> 51
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 aagcgctctc caagcaccccc cggcctgggg gtnagttctt catcccgcta ctgctgctgg 180
 gatcaggtt aataaatgga actcttcctg tctggcctcc aaagcagcct aaaaactgag 240
 gggctctgtt agaggggacc tccaccctnn ggaagtccga gggctnggg aagggtttct 300

<210> 52
 <211> 267
 <212> DNA

<213> Homo sapiens

<400> 52

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tacctgaata ccnccgcata actctcaacc nanatncntc nccatgacac tcnttctna 180
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<210> 53

<211> 401

<212> DNA

<213> Homo sapiens

<400> 53

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agagcaagtg aaaccatttc cagcctaaac tacataaaaag cagccgaacc aatgattaaa 180
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ttgagcatt taaatagtac agtaggctgg tatacattag gaaatggact gcactggagg 360
caaataagaaa actaaagaaa ttagataggc tggaaatgct t 401

<210> 54

<211> 401

<212> DNA

<213> Homo sapiens

<400> 54

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cagttgacc tttgtcttct ataataattc cttttttcc cctctttgaa tctctgtata 180
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ggtgtatccc ctttacctcc aaggaaagaa ctactagcta caaaaaatata tttggaataa 300
gcattgtttt ggtataaggt acatatttg gttgaagaca ccagactgaa gtaaacagct 360
gtgcatccaa tttattatag tttgttaagt aacaatatgt a 401

<210> 55

<211> 933

<212> DNA

<213> Homo sapiens

<400> 55

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tcctaggggta tgggtcttctt attacctggg aacacctgag ccagatgcct tacaccacga 120
tgtgcataa ggaatgcctc cgcctctacg caccggtagt aaactatccc ggttactcga 180
caaaccatc accttccag atggacgctc cttacctgca ggaataactg tgtttatcaa 240
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cacaaaaaaca cctgaaaaaaaaa ctcaagctga gttccaatgc gaaggaaaat gattggttt 780
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 cattactttt atctctgcaa atatctgcat gatagcttta ttctcagttt tctttccca 900
 taataaaaaaa tatctgccaa aaaaaaaaaa aaa 933

<210> 56
 <211> 480
 <212> DNA
 <213> Homo sapiens

<400> 56
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 gctgctccag ctgacacgtt tccagctact ggtcctgctg atgtatgtc ccctgatgt 180
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 aatggtagag tttgtccctg agatggaaatc agtttggatc ttctgcaatt ggtcacaact 360
 attcatgctt cctgtgattt catccaaacta cttacattgc ctacatatac ccctttatct 420
 ctaatcgtt tattttcttt caaataaaaaa ataactatga gcaacaaaaa aaaaaaaaaa 480

<210> 57
 <211> 798
 <212> DNA
 <213> Homo sapiens

<400> 57
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 agatgaccag agtactctta accccttaga actgttttc cttttgtatc tgcaatatgg 180
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 tgttactgcc attccattt acagttatc tgagtgaatg attatattt taaaaagtta 300
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 tatatattt aaatagattt gatagtttt taaattgctt ttttcataaa ggtatttata 480
 aagttatttgg ggggtgtctg ggattgtgtg aaagaaaatt agaaccggc ttttgcata 540
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 ggctagaata ggaagagaga aaaaatgaaa tggttgttta ctaatttat actccatttt 720
 aaaaatttttta atgttaagaa aaccttaaat aaacatgatt gatcaatatg gaaaaaaaaa 780
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<210> 58
 <211> 280
 <212> DNA
 <213> Homo sapiens

<400> 58
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 tggaccatgg tcgtgaggaa gggctcatgc cccttattt tggaaaccat ttcattctaa 240
 cagaataaaac cgagaaggaa accagaaaaa aaaaaaaaaa 280

<210> 59
 <211> 382

<212> DNA
<213> Homo sapien

<400> 59
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ccagcaccag tggcagctct ggtgcctgtg gtttctcta caagtggat tttagatatt 240
gttaatccctg ccagtcttc tcttcagcc agggtgcatc ctcagaaacc tactcaacac 300
agcactctag gcagccacta tcaatcaatttgc gaagttgaca ctctgcatttgc aatctatgg 360
ccattaaaaaa aaaaaaaaaaa aa 382

<210> 60
<211> 602
<212> DNA
<213> *Homo sapiens*

<400> 60
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actccctatc tgggaagctg gaccggacgt ttgcgggtac tgatgagctt gtgtcaagg 480
atgccaagaa ggacgatgt gttcggagg cctataagta tctagctgct ctgcacgaga 540
actgcagcca gtcatccag accatcgagg acacagcac catcatgcgg gaggttcgag 600
ac 602

<210> 61
<211> 1368
<212> DNA
<213> *Homo sapiens*

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 tggctgatgc tatacatattg ctatggacat ttagtcttgc caacacaatg gaattccacc 1260
 acactggact agtggatcca ctagttctag agcggccggc caccgcgtg gagctccagc 1320
 tttgttccc ttttagtgagg gtttaattgctg cgcttggcgt aatcatnn 1368

<210> 62
 <211> 924
 <212> DNA
 <213> Homo sapiens

<400> 62
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 tnccgnrtnc mgnactatnt caggtttgaa aaactggatc tgccacttat cagttatgtg 240
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 aatattaata ctatcatttt tccaaggatt gatgtgaaca ttaatgaggt gaaatgacag 360
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<210> 63
 <211> 1079
 <212> DNA
 <213> Homo sapiens

<400> 63
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 gaagacccca gtgatcaactt gggaaatctac cacagtccag ttttctaat ccaagaaggt 480
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<210> 64
 <211> 1001

<212> DNA
<213> Homo sapiens

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<400> 64
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<210> 65
<211> 575
<212> DNA
<213> *Homo sapiens*

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<400> 65
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gctccagtat ggcaaagggtt cttgagaatc agccatttgg taaaaaaaag atttttaaag 480
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gtgtccaga cccaaaaagg aaaaaaaaaaa aaaaaa 575

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<210> 66
<211> 831
<212> DNA
<213> *Homo sapiens*

<400> 66
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agaaaattttt ttttagtta aaacccaaatt tcactttca aatatatcttc caacttattt 180
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gcagatgaaa caaccacgtt ttctaaagtc tagggattgt gctataatcc ctatttagtt 540
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tacagagttt taatgcagta tgacatccca caggggaaaaa gaatgtctgt agtgggtgac 660
 tgttatcaa tattttatag aatacaatga acggtaaca gactggtaac ttgtttgagt 720
 tcccatgaca gatttgagac ttgtcaatag caaatcattt ttgtatttaa atttttgtac 780
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<210> 67
 <211> 590
 <212> DNA
 <213> Homo sapiens

<400> 67
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 ttctccctgg attagcagtt taaatgaaac agagttcatc aatgaaatga gtatttaaaa 180
 taaaaatttg ccttaatgta tcagttcagc tcacaagtat ttaagatga ttgagaagac 240
 ttgaattaaa gaaaaaaaaa ttctcaatca tattttaaa atataagact aaaattgttt 300
 ttaaaacaca ttccaaatag aagtggat ttaactgaccc tatttatact ctttttaagt 360
 ttgttcctt tccctgtgcc tggcaat cttcaagttc tgctgaaaat acatttgata 420
 caaagtttc tggatgtg ttagttttt tggatgtct gttttggct gaagaaccaa 480
 gaaggcagact ttcttttaa aagaattatt tctcttcaa atatttctat ctttttaaaa 540
 aaattccctt ttatggctta tatacctaca tatttaaaaa aaaaaaaaaa 590

<210> 68
 <211> 301
 <212> DNA
 <213> Homo sapiens

<400> 68
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 gagcttcgtg cttatctgaa atctaaagga gctgagattt cagaagagaa ctcggaaggt 180
 ggacttcatg ttgatttagc tcaaattattt gaaggctgtg atgtgtgtct gaaggaggat 240
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 c 301

<210> 69
 <211> 301
 <212> DNA
 <213> Homo sapiens

<400> 69
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 agcaggctga ctatgtgccg agcgatcagg acctgcttcg ctgcccgtgtc ctgacttctg 180
 gaatcttga gaccaagttc cagggacn aagtcaactt ccacatgntt gacgtgggtg 240
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<210> 70
 <211> 201
 <212> DNA
 <213> Homo sapiens

<400> 70
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<210> 71
 <211> 301
 <212> DNA
 <213> Homo sapiens

<400> 71	
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ttgttccctg cagccctccc acggaatga caatggataa aagttagctg gtacanaaag	180
ccaaactcgc tgagcaggct gagcgatatg atgatatggc tgcaagccatg aaggcagtca	240
cagaacaggg gcatgaactc ttcaacgaag agagaaatct gctctctggc gcctacaaga	300
a	301

<210> 72
 <211> 251
 <212> DNA
 <213> Homo sapiens

<400> 72	
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gtctctgtgc actctgtctt ggatgctctg gggagctat ggttggagga gtctccacca	180
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aagagccaan g	251

<210> 73
 <211> 913
 <212> DNA
 <213> Homo sapiens

<400> 73	
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gtatttgtct ccactttggt ggatacaaga aaggaaggca cgaacagctg aaaaagaagg	180
gtatcacacc gctccagctg gaatccagca ggaacctctg agcatgccac agctgaacac	240
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gtgcataaat ggtcatcata agtcaaacgt atcaattaga cttcaacctt aggaaacaaaa	360
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cacaatggaa ttc	913

<210> 74
 <211> 351
 <212> DNA
 <213> Homo sapiens

<400> 74

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aggaaggagn catggcaagc catagctagg ccaccaatca gattaagaaa nnctgagaaa	180
nctagctgac catcaactgtt ggtgnccagt ttcccaacac aatggaatnc caccacactg	240
gactagangga nccactagtt ctagagccgc cgccacccgcgttggaaacccc aactttgcc	300
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<210> 75
 <211> 251
 <212> DNA
 <213> Homo sapiens

<400> 75

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ttcatctctt tcacctgcat tttatgggt gtttgcgtga agaaaggaaa gagggaaagca	180
aatacgaatt gtactatgg taccaaatct ttgggattca ttggcaataa atttcagtgt	240
ggtgttattat t	251

<210> 76
 <211> 251
 <212> DNA
 <213> Homo sapiens

<400> 76

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aggtgaaaga gatgaaccac gactagaggc tgacttagaa atttatgctg actcgatcta	180
aaaaaaaaatttgc tttggttaa tgttaatcta tctaaaatag agcatgggtaa atatgcgtttt	240
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<210> 77
 <211> 351
 <212> DNA
 <213> Homo sapiens

<400> 77

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gaggccggag gcatgagtga gctacagtgg gaacaggctc aggactatct caagagan	120
tatctctatg actcagaac aaaaaatgcc aacagtttag aagccaaact caaggagatg	180
aaaaaattct ttggcctacc tataactggaa atgttaaact cccgcgtcat agaaataatg	240
cagaagccca gatgtggagt gccagatgtt gcagaataact cactattcc aaatagccca	300
aatggactt ccaaagtggt cacctacagg atcgatcat atactcgaga c	351

<210> 78
 <211> 1592
 <212> DNA
 <213> Homo sapiens

<400> 78

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tgcgtccatg	cagccccgccc	ggcaacggct	gcccgcgtccc	tggccgggc	ccaggggccc	180
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tcagaaatgc	aaagatgtt	gtttttgtt	tctcagtctg	ctttagctt	taactctgga	1200
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<210> 79

<211> 401

<212> DNA

<213> Homo sapiens

<400> 79

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ccagaaacgt	cacactgccc	aagatggcc	ggtacttca	ggtctggaaac	atgttgagct	180
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cgggccgcca	ccgcgggtgg	gctccagctt	ttgttccctt	tagtgagggt	taattgcgcg	360
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<210> 80

<211> 301

<212> DNA

<213> Homo sapiens

<400> 80

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aagacaggcc	taagctctag	gacgg	taat	tttgtggatt	tgttagaaac	180	
agacattctt	ttggc	ttt	cctggcactg	gtgttgc	caggtgggc	gaagtgagcc	240
accagtca	gttc	act	tgccaccaca	gat	ttc	agaatcttcc	300
t						ggtatcccc	301

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<210> 81
<211> 301
<212> DNA
<213> Homo sapiens

<400> 81
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agctctcctg gtgttactt agggatgaag gctccaggt gctccagaa atggagtcac    180
cagcagaaga actgnnttct ctgataagga tgcacccatca tttcaagct gttcgttaaa    240
gttacacagg tccttcttgc agcagtaagt accgttagt cattttccct caagcgggtt    300
t                                         301

<210> 82
<211> 201
<212> DNA
<213> Homo sapiens

<400> 82
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aagagatcca tggcaggaag tcaagagttc tgcttcaggg tcggctctggg cagccctggg    120
agaagtcatt gcacatgaca gtgatgatgt ccaggaaaac agcataactcc tggaaagtcc    180
acctgctggc cactgnntca t                                         201

<210> 83
<211> 251
<212> DNA
<213> Homo sapiens

<400> 83
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cccaaaccgg cttcccttta ccaagtaccg taaacagggg ttgagaacgt tcaatcaatt    180
tcttgatatg aacaatcaaa gcatttaatg caaacatatt tgcttctcaa anaataaaaac    240
catttccaa a                                         251

<210> 84
<211> 301
<212> DNA
<213> Homo sapiens

<400> 84
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taaaaaactca ggtatcagaa agactaaaa ggctgtttt cacttgcgtt agattttgtt    120
tccaggcatt aagtgtgtca tacagttttt gccactgctg tttccaaat gtccgatgtg    180
tgctatgact gacaactact tttctctggg tctgatcaat tttgcagttt accattttag    240
ttcttacggc gtcnataaca aatgcttcaa catcatcagc tccaatctga agtcttgctg    300
c                                         301

<210> 85
<211> 201
<212> DNA
<213> Homo sapiens

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<400> 85
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 aataaaaaag ggtgacataa ttgctaaatg gagtggagga acagtgc tcaattcttg 180
 attgggccac aatgatatac c 201

<210> 86
<211> 301
<212> DNA
<213> Homo sapiens

<400> 86
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 tttgtataaa ggtacatacc aataacaatg aacaatggac aacaaatctt attttgtat 240
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<210> 87
<211> 351
<212> DNA
<213> Homo sapiens

<400> 87
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 ctgaaagac ttgtacattt ttaaacttcc agtctcctaa ggcacagtat ttaatcagaa 180
 tgccatatt accaccctgc tttgtcaca ataaagaagc aaggattaa cactaaaaaa 240
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<210> 88
<211> 301
<212> DNA
<213> Homo sapiens

<400> 88
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 ttttctgtg gaagcacaca gttaaatcac tcaagtgtgg cgntagcgat gcttttcat 180
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 c 301

<210> 89
<211> 591
<212> DNA
<213> Homo sapiens

<400> 89
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 gctctccctc ctccccctgcc cttagcccagg gacagagttt aggaggagcc tggggcagag 180
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gaagtaggtt  cttaaagacc  ctttttagt  accagatatc  cagccatatt  cccagctcca  300
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<210> 90
<211> 1996
<212> DNA
<213> *Homo sapiens*

<400> 90

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gctaagacat	gttaaattct	taaatgccat	aattttgtt	caactgctt	gtcatcaac	180
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<210> 91
<211> 911
<212> DNA
<213> *Homo sapiens*

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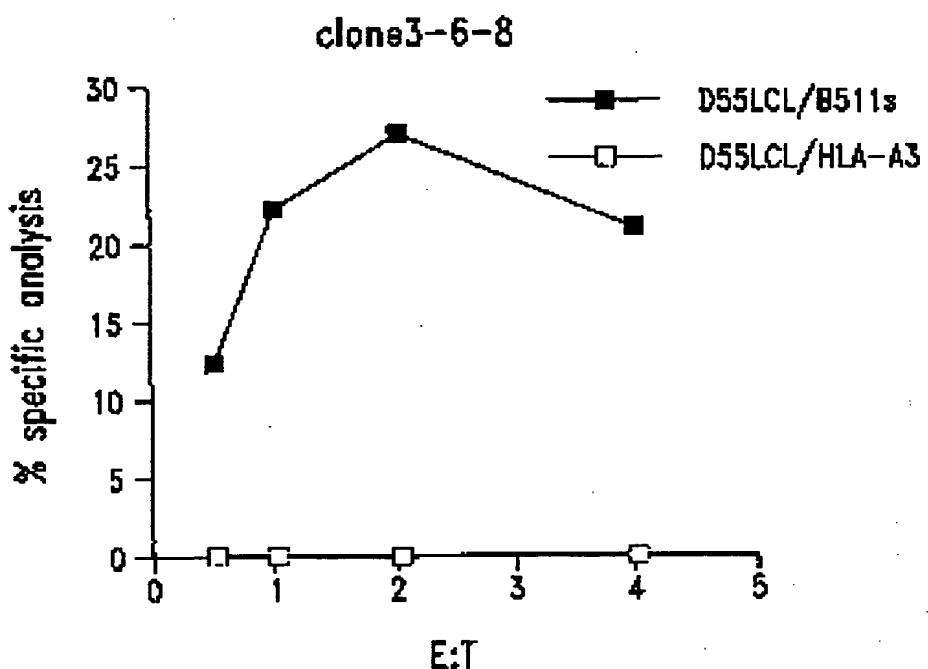


Fig. 1A

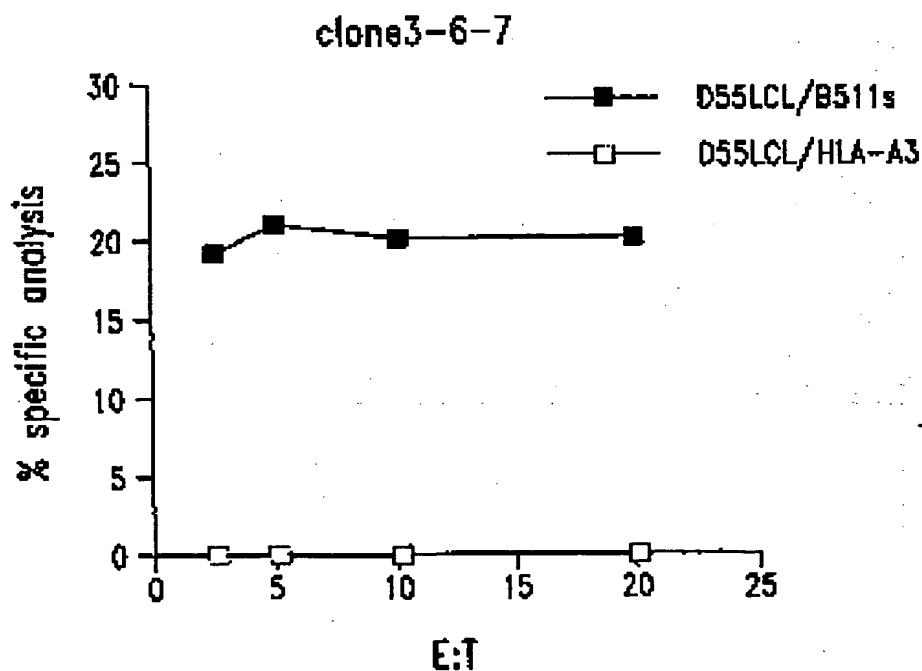


Fig. 1B

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«213» Komo sapienek

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<210> 26

<211> 400

<212> DNA

<213> Homo sapiens

<400> 26

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 ggtttctgggt ttcagattttgc aactctcaag agottggaaag ttatccatcc catccctcacg 180
 acnacnaana aatctnaacn aacnegasnac caatgacttt ttttagatct gtcacaaagac 240
 ttcagccacg aggaacacta tcccccnaa tactggggac tggaaagaga gggtaacagag 300
 aatcacagtg aatcatagcc caagatcagc ttgcctggag ctcaagctng tecgatattt 360
 acttacaggg accacttcaac agtningtngt tcaantgcen 400

<210> 27

<211> 366

<212> DNA

<213> Homo sapiens

<400> 27

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 gaattttaca ttttccagaa aacactcttt tttgtatctg tgaasagaaag tgcctccacg 180
 gctgttagact gggctgcact ggacacctgc gggggactct ggcctnagtgn ggacatggc 240

agtatggatt ttcttcacac tcagccctgig tagctntgaa agcatggaaac agattacact 300
gcaggtttacg tcatccccaca catatggac tccttagaccc gggggggccca catagtccgt 360
tatatca 366

210 28

<211> 402

<212> DNA

213 Homo sapiens

5400> 38

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ggaaagtggcc	agctgcagcg	cctccctgcag	gcagccaaag	tttttgcrtg	ggccctgtgr	120
agacacatcc	ttgcacccac	ctttacccgtc	catcangccat	gacacctgtt	gtacccactc	180
gcttngcttt	aagccccgtt	nggttgttatt	ctggggggact	tgcacacaggc	ncgtgtattt	240
gcceggctca	ttgtttccaccc	ttaaggagcat	ggcaaaaagt	ctgaggggggag	tgcattttgtt	300
anagcttcata	ggcttcatttc	agggcccttng	ctnaggccgc	ncctccatc	tccnggaata	360
acnacagggct	ttgttttttttt	actntcaata	aactgtttcg	tc		402

«210» 29

5211> 175

<212> DNA

<213> Homo sapiens

<400> 29

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cggaacgggca tgaccggctcc ggtccggctgg gtggcccaagtt tcaggcttc agcagaactg 60
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<210> 30

<211> 360

<212> DNA

<213> *Homo sapiens*

<400> 30

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ttggaaaggaaa cttracggcac agggaaagactg	ctggagaaga gaagctgtgtt agcccttting	180
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gttctttcag ggaaccaaazc ccagaatcccg	gtgcaaaagc caaacatctt ggtggggattt	300
gataaaatgcctt ttggggacctgt gatgtctgggg	tttgtgcaca ggaagagccac cagcccgctga	360

210 31

<211> 380

<212> DNA

<213> Homo sapiens

<400> 31

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agggacccaa	ttagactggg	ggaaagaaaaa	aaatctttt	ttttctggag	gttggcacct	180
gttttgtat	ccccctgttt	cagcatncc	gaaatataata	ggtttatata	caatgtttct	240
tccctgtata	ttcttttgc	tggctgcacc	ctttttttccc	gccccccagat	tgataaagtaa	300
tggaaagtgc	ctgcagtnag	ggtcacengga	gactcancat	atgtgattgt	tccntnataa	360
acttctggtg	tgataacttcc					380

<210> 32
<211> 440
<212> DNA
<213> Homo sapiens

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<400> 32
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cttcacccctt ggggtggatg atgtgacutt cctnngggga ctggggaaagg gacaagggtt 180
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caggggagac cgtnccatc gggatgtgtg ctggctgtg tacgtgggtg tgcagtgcac 300
gtganaagca cgtggccggt tctggggcc atgtttgggg aaggaagtgt gcccncacc 360
cttggggaaac ctcaagtcccn gtacccccctt gcccctggcac agcngcatnc acttcaaggg 420
caccctttgg aqgttgggggt 440

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<210> 33
<211> 345
<212> DNA
<213> *Homo sapiens*

<210> 34
<211> 440
<212> DNA
<213> *Homo sapiens*

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<400> 34
tgtaabtttt ttatggaae scaaatatac aacctggaaat ggattttgag gcaattgtg 60
ccataagcag atttaagtg gtaaaceaa gtttaaaaag caagtcacaa taaaagaaaa 120
tgtttctgtt acaggaccag cagtacatca aatactgtta cgagttacctg gataatacac 180
ccgttttgca atagtgcacat tttaaagtac atattgttga ctgtccatag tccacgcaga 240
gttacaactc cacacactcaa cccaaacatg ctgacagttc ctaaagaaaa ctactttaaa 300
aaaggcataa cccagatgtt ccctcatttg cccaaactcaa tctnagtta gatgtgcaga 360
agggcttana ttttcccaaga gtaagccca tgcaacatgt tacttgcata attttctaaa 420
atagggtttt eqqacaaatqa 440

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<210> 35
<211> 540
<212> DNA
<213> *Homo sapiens*

<400> 35
atagatggaa ttatataaagc ttttcacatgt tgatagcaca tagttttaaat tgcatccaae 60
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ctgtggcttt taaaatttgg ttttcataag ataaatttataa ctgtaaatgtaaa tctagccatg 180
cttttataaa atgttttttagg tcactccaaag cttggcagtt aatatttggc ataaacaata 240
ataaaaacaat cacaattttaa taaaatcacaat atacaacatc atagggccata atcatataca 300
atataaqqqa aaaaatggaa gtgttgatgtt agcagttatt agaatagaat accttggcc 360

ctatgcataat atgtctagac acttttgcattt acttcagccat gacattcagt ttttca>i. 420
 agggaaacagg ttctacagta tcattttaca gtttccaaaca cattgaaaaac aagttagaaaa 480
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<210> 36

<211> 555

<212> DNA

<213> Homo sapiens

<400> 36

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 tgcgtgcgg cattgcaaaac gccatgtgtg gaeactggag gggaaatatt ccattttggc 180
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 gacccctgtg gaggaaagaa aactctgtct ggcatgaccr acagtttttt gactggaaac 480
 ctttcaaccct cttgggttcaa gctttgttct gacccctgtgaa tntgcttggg cncctgggtng 540
 gncctgggtt cttaaa 555

<210> 37

<211> 280

<212> DNA

<213> Homo sapiens

<400> 37

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 ctctaaaaaa tatctgtact tctataataca ttgtatntcaa gaaaatgacg gtcacacgacc 180
 aggtgtaaactg ccccnagctc tgcataaccc> gttctacagg gaggctgtcac ccactccatg 240
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<210> 38

<211> 303

<212> DNA

<213> Homo sapiens

<400> 38

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 ctccacacag gtgaactcgg aagacaaagg cgtttggct tagctggtn aagctatcag 180
 gaccaattac aatgacngat acgtatnagat ccgcuntcac tggggtagca atgtccctggg 240
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 taa 303

<210> 39

<211> 300

<212> DNA

<213> Homo sapiens

<400> 39

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 atcaaataccc arcaagatnt tgggttttgc caccgaattt tgggtttgggt tccctnaaag 120
 aactcttttgc tgcataatnac tnaaagttag gttctgggtac cttttacatg atttcccaaga 180

cctccanatgg gctaacacgc ttctcttctc cagcagtctt cctntccgtg aagttacott 240
 ccagattgtt acatggaaat gaaacaaatgg ggagccctcag ctngatttaa atctggagaa 300

<210> 40

<211> 318

<212> DNA

<213> Homo sapiens

<400> 40

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 tgggtgttg ggcgaccaag gcccattccgg agtcttgcgtc ctctatgagc tctcgcccat 120
 gatggtgaaag ctgacggaga agcacaaggta cttcaacccac ttctgacag gtgtgtgagc 180
 catcatggg ggcattgttca cagtggtctgg actcatcgat tctgtcatct accactcaggc 240
 acgagccatc cagaaaaaaa ttgatctngg gaaagacnagg tagtcacccct cggtncttcc 300
 tctgtctctt ctttctcc 318

<210> 41

<211> 302

<212> DNA

<213> Homo sapiens

<400> 41

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 cttggccatgtt atgttcccca tccggacaca gycgtgcgtt ctctgtatgt gtcaaagctg 120
 ccatnccat ctcggtaacc tacatctact ccacaatgtc tatattcaat gcagggctct 180
 ataatnagtc cataatgttca atgcctggcc caagacnntat ggcctgagtt tatccnaggc 240
 ccaacnattt accagacatt ctttcttccat taaaaacggc tntctttccc tggcaaaaga 300
 tc 302

<210> 42

<211> 299

<212> DNA

<213> Homo sapiens

<400> 42

cttaataagt ttaaggccaa ggcccggtcc attcttctag caactgacgt tgccagccga 60
 gttttggeca tacccatgt aatgtgggtt gtcacttttgc acatccctac ccattccaaag 120
 gattacatcc atcgagtaggg tcgaacagctt agagctgggc gtcggggaaa ggttattact 180
 ttgtcacac agtatgtatgt ggaactcttc cagcgcatacg aacacttntat tggaaagaaa 240
 ctaccagggtt tcccaacaca ggtatgtatgtt tttatgtatgtc tttatgtatgtc 299

<210> 43

<211> 305

<212> DNA

<213> Homo sapiens

<400> 43

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 ctttcattgg caatagcaca gcccattccgg agtcttccaa ggcgcattctcg gagcaggatca 120
 ctgcctatgtt ccggccggaaag gcccattccac actggatcac acggcggggc atggacaaaga 180
 tggagttccac cgaggctgag agtacatgtt acgacccatgt ctctnagtat cagcagttcc 240
 gggatgcccac cgcagaaaana ggaggaggat ttggtnagg aggcgcagaaga agggaggctg 300
 aggca 305

<210> 44

<211> 399

<212> DNA

<213> Homo sapiens

<400> 44

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 tggaaacgaa cgaaaacnoga tnaatctcg tttctgtat taaagcact cgatncccg 120
 cagacacago tttttttttt ngatttagcgc aacagggaga aagaanatgc 180
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 aeaaggcgcgc ggcggcgnaa tttttttttt ggcggcgnaa gatcttgac 300
 ttctttatka ggccaaacgaa aaaccccgaa ananaggcct tacnataact tngaaaantc 360
 tccngccnaa aaaagaaaga ayctttcnga ttcttaacc 399

<210> 45

<211> 440

<212> DNA

<213> Homo sapiens

<400> 45

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 accagtacca ataaacatgtc cagtggcagt ggcggccatca gtgggtggctt cagtgtctgtt 120
 gddagccctga cccggcactct cacatttggg ctatctcgatg gctttgggtgg agctgggtggc 180
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 taggaaggcc caatgtggag aangatgtgn anagtgtgc aagacactgc ttttggcatt 360
 ttatcccttt ctgtttgttg gatgtcaatt gaccctttna ntttcttta ctgtgtttt 420
 canatatngt tttatctgtcc 440

<210> 46

<211> 472

<212> DNA

<213> Homo sapiens

<400> 46

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 ttttctctgt tccttttcaat agcaaaaact gttcaaaaga gttgtgtatt attttcattt 120
 ccacttttcc acccccccattc tcccttcaat taactcttcc tcatcccat gatggccatca 180
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 cctcataaca atctctttcc cagcccttac tttttttttt tttttttttt tcccaagggtc 360
 cttaggttcag atgtatgtgtt gttcaaccct gttttttttt gaaaggctgt 420
 aaaaatgtcc atnctgtcc tttttttttt tttttttttt tttttttttt tt 472

<210> 47

<211> 550

<212> DNA

<213> Homo sapiens

<400> 47

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 aggttcgggag cttoctcagt ggtctgtatg aggtatggatg acggggactg gtggggaaatc 120
 gggggggccctg tctgggtgcg agggcgacgc ttttttttttccatccatg cccggccatg 180
 gtggagctgg ggcgtcgttc catcgtgtat gaaactggccca ttttttttttccatgggtccct 240
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cttcagtgtc ctgtgtttaa gctgtttagga tttacntgggg tacatttta ctaccggacgg 420
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aaagcttttgc tgctcaggtt caaggccaaat tttgtaaaatgtt aacaaatgtgc ctggggatgg 540
gaatttttgtct 550

<210> 48
<211> 214
<212> DNA
<213> Homo sapiens

<400> 48
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acaaaccctttt caacttcaag ctgggtcatct gtctgtatua gggtttcttc negagtggga 120
agttttgtgtt cagttttbaac gtggggccagg gttacccgca tgatcccccc aaggtgaagt 180
gtgagacnat gttttatcac ccnnacattg aact 214

<210> 49
<211> 267
<212> DNA
<213> *Homo sapiens*

<4D0> 49
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agtttttagg acacatctatgc acaaatagtac qatggagaaat ttttttttggg tnaactctatg 120
gttngaggaaac ttaatccaaac cggagctttt gtgaaggctca yaanacagggg gaggaaatct 180
tggcaaggaa tggagaatnggaa gtttgcaaat tgcagctaga gttaatngtt nttaatgggg 240
atgcattttgtt atctcccaaaa qaaagttt 267

<210> 50
<211> 300
<212> DNA
<213> *Homo sapiens*

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<400> 50
qactgggtca aagctgcatg aaaccaggcc ctggcagcda cctgggaatg gctggaggtg 60
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ttgggtcttt ctgagcttgt ttccctgtctg ggtgggacag aggacaaagg agaagggagg 180
gtctagaaga ggcaagccctt ctttgtcttc tggggtnaat gagcttgacc tanagttagat 240
ggagagacca aaaaaccttca atttttatc tccataanat gttcnaagta tatntntacc 300

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<210> 51
<211> 100
<212> DNA
<213> *Homo sapiens*

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<400> 51
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cccttatttc tagttggtcc aggatttaggg atgtggggta tagggdattt aatctcttc 120
aagcgctctc caagcacccc uggtctgggg gttagttct catcccccta ctgctgtgg 180
gatcaggtt aataaatggc actttcttg tctggccccc aaagcagccct aaaaactgag 240
gggtctcggtt acaqqqqacc tccacccctnn ggaagttccga ggggctnnggg aagggtttct 300

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<210> 52
<211> 267
<212> DNA

213 *Homosapiens*

52

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cacctatcaa gggaaacnnacu tgattgcctc tattnaacaat atatatcgag ttntctatact 120
tacctgeata ccncrcgcata actctcaacc nnnatnntc nccatgcacac tcnttcttta 180
atgcctatccc cgaatttttcc atttatateng tgatgttcggc cctgntnata tattcaggaaq 240
gtatatnncn tcaactgccccgaa nncaang 267

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<210> 53

5211 401

<212> DNA

<213> Homo sapiens

<900> 53

aggttttagc atcatgtaga agcaaaactgc acctatggct gagataggtg caatgaccta 60
caagattttg tgttttctag ctgtccagga aaagccatct tcagtctgtc tgacacgtcaa 120
agagcaagtg aaaccatttc cagcctaaac tacataaaag cagccgaacc aatgataaa 180
gacccctttagt gctccataat catcattata tatgccttcaa ctcatgtgtc ctttttattt 240
tatatacagg attaaaatca acatcaaatac atcttattta ratggccatc ggtgtgtgaaa 300
tttggatattt tataatgtac agtaggctgg tatacattag gatggact gcactggagg 360
caataaaaaa actaaagaaa ttatgtatggc tggaaaatgtct t 401

«210» 54

5211> 491

<212> bDNA

<213> Homo sapiens

<400> 54

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ccccaacacaa tggataaaaaa cacttatagt aatatggggac attcaactata atgtatctaag 60
aagctacagea ttgtcatagt tggtttccctg ctttacaaaaa ttgtcccaaga tctgtaatgc 120
cagtttgacc ttgtgtttttttaataatatttc ctttttttcc ecctctttgaa tctctgtata 180
tttgcattttt aactaaaaattt gttcttttaa atattctgaa tctctggtaat taaaagtttg 240
ggtgttatttt ctttacatcc aagggaaaggaa ctactagata caaaaatata ttgtgatata 300
gcattgtttttt ggtataaagt acatatttttgc ttgtggaaagaca ccagactgaa gtaaaacagct 360
gtgcattccaa ttattttatag ttttgtaaagt aacaatatgt a 401

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«210» 55

211 933

4212 DNA

<213> Homo sapiens

<400> 55

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tgtgcataaa ggaatgcctc cgccctctacg caccggtagt aaactatccc ggttactcga 180
caaaaaaccatc acctttcccg atggacgctc ttatccctca ggaataactg tggttatca 240
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gagatttctcc agggaaaaatt ctgaaaaaaat tggccataatt gagtgtaaaag tggcagtggc 360
tggatttaagg aactgcattg ggcagcattt agaccactca agqccaccca gctgtgtca 420
atcaactctg ctccgcctca agctgggtcc agtccaaaggaa tggaatccat tttccatacc aaaaaggata 480
tgttgcctca agtccaaaggaa tggaatccat tttccatacc aaaaaggata 540
gtccctttcg tataagaatt aakgagacaa tttccatacc aaaaaggata 600
ataataatac aaaaatatacg tataatgggttg tttccatacc aaaaaggata 660
tgactgggtt tgcacatccat taacagtaat tttccatacc aaaaaggata 720

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e2102 56

<211> 480

<212> DNA

<213> Homo sapiens

<400> 56

5210a 57

211 798

<212> DNA

213 Homo sapiens

<400> 57

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gactaaattt	gtgtatgtgg	aaatgtgaaaat	agttaaacacc	ttgcacggacc	aaacgaaecgc	120
agatgaccag	agtaactrta	acccttttga	actgtttttc	cttttgtata	tgcaatatgg	180
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tgttactgcc	atccctattt	acatgtatattt	tgatgtaaatg	atttatatttt	taaaaaggta	300
catggggctt	ttttgggttgt	cctaaactta	caaaacattcc	actcattctg	tttgtaaatg	360
tgattataat	ttttgtata	atttctggcc	tgtttgaagg	aaattttgaga	ggtctgcatt	420
tatataattt	aaatagattt	gataggtttt	taaatttgctt	tttttcataa	ggtattttata	480
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ggctagaata	gaaegagaga	aaaaatgaaa	tggttgttta	ctaattttat	actcccatte	720
aaaaatttta	atgttaagaa	aaacotttaat	aaacatgtatt	gtcaatatg	gaaaaaaaaa	780
aaaaaaaaa	aaaaaaaaa					798

<210> 58

5211> 280

<212> DNA

<213> Homo sapiens

<400> 52

52102 59

-211- 382

<212> DNA

«213» Homo sapiens

4002 59

219 60

<211> 602

6212a DNA

213 *Homo sapiens*

<400> 60

52193 61

211 1368

e2127 DNA

213 *Homo sapiens*

<400> 61

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5210-62

52112 924

<312> DNA

<213> Номо варієнв

<400> 62

$\leq 21.0 \geq 63$

€2112 1072

62123 DMA

4333 Кропа вагіні

<400> 63

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 tggaaatccag ctggcagcta taegcaccgt tgaaaactct gacaggctt gtgcctctt 180
 tattaaatgg cctcacatcc tgaatgcagg aetgtgttcg tttaaataaa cattaatctt 240
 taatgttggaa ttctgaaaaac acaaccataa atcatagttg gtttttctgt gacaatgtac 300
 tagtacatta ttctccac agcaaaatctt cttttccaga aggtggaaat tgtatttgca 360
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 atgacccgtta ataaatctcat aatttcttgc tctttttttt aggttagctat aatatggggg 1020
 aataacccccc ttttttttttcaacatctgs gctgtccaaa gctaaagttagg aacacaccc 1079

<21D> 64

«211» 1001

<212> DNA

<213> Homo sapiens

400 64

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gttcaactatg gcctatctac aatgtcaacta aaaaactagat tttatccctt tccacctgtg 180
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ctatgtatata cttatgtaca ttccatccaa aaaaaaaaaa a 1000

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<210> 65

211 575

<212> DNA

213 Homo sapiens

<400> 65

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cttggctact	tcataccat	gucttaaaga	ggggcragttt	ctcaaaagca	gaaacatgccc	180
gccagtttcc	aagttttctt	cctaacttcc	tttguatgtt	aggggcggctg	gcccccaatg	240
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ctgtcattac	ttagattccc	gatttttccc	aaagggtgtt	atttacaaaag	aggccageta	360
atagccagaa	atcatgaccc	tgaaagagag	atgaaatttc	aagctgtgag	ccaggccagga	420
gttccatgt	ggcaaaagggtt	citgagaatc	agccatttgg	tacaaaaaaag	atttttaaag	480
cttttatgtt	ataccatgga	gcctatgeaa	ggctatggat	tgtttaaagaa	ctttttaaa	540
gtgttcaga	ccccaaaaagg	aaaaaaaauu	aaaaa			575

<210> 66

211 831

<212> DNA

<213> Home September

<400> 66

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atggggctcc ttctgtctaaa cagccacatgt gaaatggttt aaaagcaagt cagatcagg 60
gattttgtaaaa atgttattttat tctgtacatg tatggggcttt taatccccac ctagaaaggag 120
agaaatatttc tttttagtta aaaccaaattt tcaacttttca aatatacttc caacttattt 180
atgggtgttc actcaattgc cttatataatat atataatataat gtgtgtgtgt gtgtgtgcgc 240
gtgagcgcac gtgtgtgtat ggcgtgcgcat gtgtgtgtat gtgtattatc agacatagg 300
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tctatgtgcc tgtatttccr tttttagtgc tgccacaacat gttaacatataat tagtgtaaaa 480
gcagatgaaa caaccacgtg ttctaaatgc tagggatgtgt gtataatcc ctatgtatgtt 540
caatataac cagaatttctt ccatgtgtttt tgccaccaac tcatatattt gttatgtaaa 600

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tacagagttt taatgcggta tgacatccca caggggaaaaa gatgttgtgt agtgggtgac 660
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 tcccatgaca gatttgagac ttgtcaatag caaatcattt ttgtatataa atttttgtac 780
 tgatttggaaa aacatcatca aatactttt aaaaataaaaa aaaaaaaa 831

<210> 67

<211> 590

<212> DNA

<213> Homo sapiens

<400> 67

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 ttctccctgg attagcagtt taatggaaac agatgttcatc aatggaaatga gtatttazaa 180
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 ttaaaacaca ttccaaatag aagtggatcc gaaatggaccc tattttatct ttttttaagt 360
 ttgtttccctt tccctgtgc tggatcaat cttcaatgtt tggatggat tttttttttt 420
 caaagtttttgc tggatgtgtt ttagttttt tggatgtgtt gtttttggat gaaatggccaa 480
 gaaatggatcc tttttttttttaa aaaaattttt tctctttcaaa atatttctat cttttttttt 540
 aattttttttt ttagggctta tataccatca tattttaaaaa aaaaaaaa 590

<210> 68

<211> 301

<212> DNA

<213> Homo sapiens

<400> 68

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 gagcttcgtt cttatctgaa atctaaagga gctggatgtt cggatggatcc ctggaaagggt 180
 ggacttcatg ttgtatgttgc tcaatattttt gaaatggatgtt atgtgtgtct gaaatggatgtt 240
 gatggatgtt ttagggatgtt gatggatgtt gggggatccctt ctctttgtatcc cggaaatccna 300
 c

<210> 69

<211> 301

<212> DNA

<213> Homo sapiens

<400> 69

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 agcagggtgttca tttatgtgtcc agtggatgttcc acctgtgtcc ctggccgtgtc ctgtacttctg 180
 gatgtttgttca gatggatgttcc agtggatgttcc acatgtgttca gatgtgttcc 240
 gatggatgttcc tggatggatgttcc agtggatgttcc agtggatgttcc gatgtgttcc 300
 t

<210> 70

<211> 301

<212> DNA

<213> Homo sapiens

<400> 70

cgccatctttt ctcggggcagc ggaaggcggtcg gggcggtcg agaagggtggcc taaaatctcg 60

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gctgtgggtg aatggaaatgt gccccgaacca agcagactgc tcgttaagtcc acgggtggga 120
aagcccccccg caaaccagctg gcccacggaaag ccggccaggaa aagccgttccc tcttacccggcg 180
ccgttggaaat gcttcattgc t 201

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<210> 71
<211> 301
<212> DNA
<213> *Homo sapiens*

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<400> 71
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tggatgtgg gcttaggaag ggagggtca tctcgctcg ggcttcgctc ggaagggtct 120
ttgttccctg cggccctcccg ccgggaatga caatggataa aagtggatgtg gtacanazag 180
ccaaactcgc tgagcaggtt gagcgatata gatgatatggc tggccggccatg aaggcagtc 240
cagaacaggg gcatgaactt tlcacacgaa agagaaatct gctttctggc gcctacaaga 300
a

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<210> 72
<211> 251
<212> DNA
<213> *Homo sapiens*

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<400> 72
cttgggggggt gttggggggag aqactgtggg octggaaata aqacttgtat cctctaccac 60
caaccgtgtac octtagectgc acctgtccac atctctgcaa agttcaagtt ccttcccccag 120
gtctctgtgc actctgtttt qgatgtcttg gggagctcat gggtgggagga gtctccacca 180
gaggggaggct caggggactg gttggggccag ggatgaatat ttgagggata aqacttgtat 240
aaqaqcacan q 251

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<210> 73
<211> 913
<212> DNA
<213> Homo sapiens

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<400> 73
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caaaaaatccctt ggtctcccat cagctggaaat taatggtaggtt ctgtgtatct ttgegatcat 120
gtatccatgtct ccactttgggt ggatccaaaga aaggaaaggca cgaacagcttg aaaaagaagg 180
gtatccacacc gtcggcagctg gaatcccgacca ggaaccccttg agcatgccac agctgaaacac 240
ttaaaaagagg aaagaaggac agctgtctttt cattttatttt gaaaggcaaat ttttttgaaa 300
gtgcataaaat ggtcatcata agtccaaacgt atcaatttaga ctttcacaccc agggaaacaaa 360
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atttggtaca aatagttacaa tccgttttttgc ttttccctttt tcccttttcc agatccaaacac 480
caaaaaatccat gcaagggtgaaa gagatgaaacc acgacttagag gctgacttag aattttgc 540
tgactcgatc taaaaaaaaaat tatgttggtt aatgttaatc tatctaaaaat agagcatttt 600
gggaatgtttt ttcaaaaaaag gtcagaatcaat agtcatacag ctggaaaaatg cctgaaaaaa 660
aagaatgtttt aagaatgtata ataaacccctttt caaaacccac aatgcagctt agttttccctt 720
tattttatgg tggtcatgaa gactatcccccc attttccat aaaaatccccc ctccatactg 780
ctgcattatgt gcacaaaaaga ctctaaagtgc caccagacag aaggaccaga gtttctgtatt 840
ataaaacaatgt atgtgggtt aatgtttaaat gagaacatgt gatatggatg gtcagcccaa 900
cacaatggaa ttc 913

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<400> 78

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tgcgttcatg	cagccccggc	ggcaacggct	ggccgtcccc	tggccgggc	ccagggggcc	180
ggcccccacc	gcccccgctgc	trgcgtgtct	gtgttgcgc	gccccgggtgg	cgccgcggcc	240
gggggtccggg	gaccccgacg	accctggggca	gcctcaggat	gtgggggtcc	cgccgcaggt	300
cctgcggcgg	gcggggcgccg	cggcgcttca	tttcttcaac	ttccgggtccg	gctcgccccc	360
cgcgctggc	gtgtctggccg	agggtgcagg	ggggccggcg	tggattaaatc	ccaaagaggg	420
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ataatataat	ttcgatgaaa	gtaaattata	ggaaaaaaat	taactgtttt	aaaaagaaact	1500
tgattatgtt	ttatgtttt	aggcgtgt	tccattttaa	tttgcgtac	acttttaat	1560
aatgttttcc	atttctaaaa	aaaaaaa	aa			1592

<400> 79

<211> 401

<212> DNA

<213> Homo sapiens

<400> 79

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tcttctggaa	ctatgtgtt	gttcttttgc	ctgcctgtc	ggccagcato	120
ccagaaacgt	cacactgccc	aaagatggcc	ggtaatccaa	ggtctggaaac	180
gagttccatgt	gacatcata	agtcccaag	tagcagcat	ttccaggtgt	240
tgcttaggagc	aaaatgtga	tggagacat	tggcaccat	ccggatccac	300
ggggccggcc	ccgcgggtgg	gttccagctt	ttgttccctt	tagtgagggt	360
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<210> 80

<211> 301

<212> DNA

<213> Homo sapiens

<400> 80

aaaaatgtaaa	catactattt	agcagcaaga	ggctgtgagg	atgggggtag	aaaaggcatt	60
ctgagagagt	tctagaccga	cccaggctt	gtggcacact	atacgggtca	ggaggggtgg	120
aagacaggcc	taagetcttag	gacgtgtaa	ctgggggtca	tttgcggatt	tgttagaaac	180
agacatctt	tggccctttt	cctggcactg	gtgttgcgg	cagtgggca	gaatgtggcc	240
accaggcact	gttcagtcat	tgccaccaca	gtcttcacgc	agaatcttcc	ggtaatcccc	300
t						301

<210> 81
<211> 301
<212> DNA
<213> *Homo sapiens*

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<400> B1
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agctcttcttgg ttgttgcatt agggatgaag gtcggggct gtcggcagaa atggagtcac 180
cagcagaaaga actgtttttt ctgtatggaa tggccacca tttttaagct gttcggtaaa 240
gttacacagg tccttcttgc agcagtaagt accgttagct cattttccct caagcgggtt 300
t

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<210> 82
<211> 201
<212> DNA
<213> *Homo sapiens*

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<400> 82
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engagatccaa tggcagggaaag tcaagagttc tgcttcagggg tcgggtctgggg cagcccttggaa 120
agaagtcaatt gcacatgacaa gtgtatgatgtg ccaggaaaaac agcatatcc tcggaaatgtcc 180
acctgtcaaaat cactgtttca t 201

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<210> 83
<211> 251
<212> DNA
<213> Homo sapiens

<210> 84
<211> 301
<212> DNA
<213> *Homo sapiens*

```

<400> B4
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taaaaaactca ggtatccagaa agactcaaaa ggctgtttt cactttgttc agattttgtt 120
tccaggdatt aagtgtgtca tacagttttt gccactgttg ttttcaaat gtccgatgtg 180
tgctatgact gacaactact tttctctggg tctgtatcaat ttgcgatgtt accattttag 240
ttcttaeggc gtcnataaca aatgtttcaa catcatcagc tccaatctga agtcttgctg 300
c

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<210> 85
<211> 201
<212> DNA
<213> *Homo sapiens*

<400> 85
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 agtcacacca taaaggagtt tatcccttcaa aggagtgaaa gacattcaaa aaccaactgc 120
 aataaaaaaaag ggtgacataa ttgtctaaatg gagtggaggaa acagtgccta tcaattcttg 180
 attggggccac aatgatatac c 201

<210> 86
 <211> 301
 <212> DNA
 <213> Homo sapiens

<400> 86
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 cccttttgcg atatcactt tatgactatc ttctcaaaaa cgtgacatcc gattataaca 120
 cataaaactac atttagtt gttaagtcac ttgttagtat aatatgttt tcatctttt 180
 ttgtataataa ggtccatacc aataucaatg acaatggac aacaaatctt attttgat 240
 ctttccaaatg taaaattcat ctctggccaa acaaaatata accaaagaaa agtaaaaacaa 300
 t 301

<210> 87
 <211> 351
 <212> DNA
 <213> Homo sapiens

<400> 87
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 aaaaaacaaca tttggcttt ctaaaaaaa gactttttt aaaaatcaat tccctcatca 120
 ctggaaaggac ttgtacatcc ttatctcc agtctccctaa ggcacagtt ttaatcggaa 180
 tgccaaatatt accaccctgc tgtagcanga ataaagaaac aegggattaa cacttccaaa 240
 aacngccaaa ttctgtggcc aatcattgg cattttaaa aaggataaa aaaaenggnt 300
 aegggggggga gcaatttaag taaaagaangg ccaagggtgg tattggcngga c 351

<210> 88
 <211> 301
 <212> DNA
 <213> Homo sapiens

<400> 88
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 ttttctggtg gaagcacacaca gtttaatttac tcaagtgtgg cgtttagcgtat gttttttcat 180
 gggtgtcatcc atccacttgg tgaacttgcg cacttgcattg aacactccctg ggttcatggg 240
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 c 301

<210> 89
 <211> 591
 <212> DNA
 <213> Homo sapiens

<400> 89
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 gtcctccctt ccccccgtcc ctggccagg gacagatctt agggaggcc tggggccagag 180
 ctggaggcag gaagagagca ctggacacac agctatgttt tggatgggg aagagatag 240

gaatgggtt	ctttaaaagacc	cttttttagt	accagatatac	cagccatattt	ccccggctccs	300
tatccaat	cattcccat	ageccaaatgc	ctctctgttc	ttccctctact	accatttttt	360
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<210> 90

<211> 1996

<212> DNA

<213> Homo sapiens

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<211> 911

<212> DNA

<213> Homo sapiens

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211 1710

<212> DNA

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<400> 92

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211 251

<212> DNA

<213> Homo sapiens

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<211> 738

<212> DNA

<213> Homo sapiens

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